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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,455	06/01/2006	Michal Amit	32059	2318

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
09/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,455	AMIT ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52,55-75 and 78-84* is/are pending in the application.

4a) Of the above claim(s) *62-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,55-60,74,75 and 78-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/26/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 6/2/09, has been entered. Claims 52, 55-75, 78-84 are pending; claims 62-73 are withdrawn; claims 52, 55-60, 64, 78 are amended; claims 52, 55-60, 74, 75, 78-84 are under current examination.

Information Disclosure Statement

Applicants' IDS, filed 5/26/09, has been considered.

Election/Restrictions

Claims 61-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/28/08.

Applicant's election of Group I (claims 52, 55-60, 74-74, 78-84) in the reply filed on 11/28/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The Examiner notes that claims 83-84 were inadvertently left out of the restriction requirement, mailed 9/5/08. The claims are found to be part of the elected group and will be examined accordingly.

Applicants further elected SEQ ID NO: 34 for a species election. The Examiner withdraws the species restriction requirement and all species are examined.

Claim Objections

The objection of claim 59 is withdrawn in view of amendment to the claim to correct the spelling of "isolated".

Claim Rejections - 35 USC § 112

The prior rejection of claim 78 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants' amendment to the claim which now has antecedent basis.

Claim Rejections - 35 USC § 102

The prior rejection of claims 52, 55, 56, 58-60, 74, 75, 78-80 are rejected under 35 U.S.C. 102(a) as being anticipated by Amit *et al.* is withdrawn in view of the Itskovitz Eldor Declaration stating that Hanna Segev and Dorit Manor were not inventors.

The prior rejection of

1. Claims 52, 55, 56, 58-60 under 35 U.S.C. 102(a) as being anticipated by Zwaka *et al.* is withdrawn

2. Claims 52, 55, 56, 58-60 under 35 U.S.C. 102(e) as being anticipated by PGPub US 2006/0128018 A1, is withdrawn.

These rejections are withdrawn in view of the Amit/Itskovitz Eldor Declaration stating that Zwaka and the '018 document are not prior art because the instant invention was reduced to practice prior to February 7, 2003, and point to Amit *et al.* as evidence of an earlier publication date.

Claim Rejections - 35 USC § 103

The following rejections are withdrawn:

1. Claims 74, 75, 78-79, 82-83 under 35 U.S.C. 103(a) as being unpatentable over PGPub US 2006/0128018 A1 (Published June 15, 2006; Filed

February 6, 2004 when taken with PGPUB US 2002/0081668 A1 (published June 27, 2002; filed November 30, 2002).

2. Claim 84 under 35 U.S.C. 103(a) as being unpatentable over PGPub US 2006/0128018 A1 (Published June 15, 2006; Filed February 6, 2004 when taken with PGPUB US 2002/0081668 A1 (published June 27, 2002; filed November 30, 2002) as applied to claims 74, 75, 78-79, 82-83 above, and further in view of PGPub US 2005/0054092 A1.

These rejections are withdrawn in view of the Amit/Itskovitz Eldor Declaration stating that the '018 document is not prior art because the instant invention was reduced to practice prior to February 7, 2003, and point to Amit *et al.* as evidence of an earlier publication date.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52, 55, 56, 58-60, 74, 75, 78-80, 82 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ratcliff (**Transgenic Res.**, 1: 177-181, 1992, IDS) when taken with Thomson *et al.* (**Science**, 282: 1145-1147, November 6, 1998), and US Pat. No. 7,390,659 (Issued June 24, 2008) in further view of Elsea *et al.* (**ILAR Journal**, 43(2): 66-79, 2002).

Applicants' Arguments. Applicants argue that a *prima facie* case of obviousness has not by combination of the prior art. Applicants argue that Ratcliff teach homologous recombination in mouse ES cells, techniques which cannot be used without major modifications on human ESCs in order to generate human ESC cell lines harboring genetic mutations, even in view of Elsea, who merely state that there is a need for human ESCs as a model for genetic disease, and the '659 patent which teaches of methods of differentiating ES cells. Applicants argue that it was well known in the art that, in contrast to mouse ESCs, which can be subject to electroporation protocols, human ESCs do not survive electroporation well and that human ES cells cannot be efficiently cloned from a single cell. Thus, Applicants argue that it is conceivable that screening for rare combination events in human ESCs is extremely more complicated than in mouse ES cells, let alone generation of human ESC lines from a single ESCs having the targeted recombination. Applicants provide Eiges (2001) and Amit (2000) as evidence of these arguments. See p. 13 of the Response.

Applicants further provide the Amit Declaration as support to show that protocols established for mouse ES cells cannot be used without major modifications on human ESCs because of these differences. Applicants further point to Zwaka (2003, previously cited) who state that significant differences between mouse and human ES cells have hampered developments of homologous recombination in human ES cells, and that neither Thomson nor any other researcher skilled in the art of hESCs have taught or suggested, prior to conception of the claimed invention,

how to obtain human ES cell lines which harbor genetic mutations as claimed. See p. 14 of the Response.

Applicants argue that it is their position that due to the major differences between mouse and human ES cells, the lack of guidance in Ratcliff, Thomson, Elsea, and the '659 document, with respect to what modifications are needed for performing homologous recombination in human ES cells, one of ordinary skill in the art would not have been motivated to apply the technology of producing specific disruptions in mouse ES cells on human ES cells to thereby generate human ES cell lines carrying a disease-causing mutation in a genomic polynucletodie sequence. See p. 14, 3rd ¶ of the Response.

Applicants argue that in sharp contrast to the genetically modified mouse ESCs taught by Ratcliff, which were generated by homologous recombination, the present inventors have uncovered that human ESC lines that carry disease-causing mutations can be established from human blastocysts which are selected based on the presence of the disease causing mutation. See p. 14, last ¶ of the Response.

Response to Arguments. These arguments have been fully considered, but are not found to be persuasive. Applicants' arguments and the Amit Declaration appear to focus upon the cloning efficiency of human ES cells to produce cell lines. However, the claims are not directed to a clonal cell line, and encompass any human ES cell line. Thus, these arguments not fully within the scope of the claimed invention. Additionally, Thomson provide sufficient guidance with regard to the production of a ES cell line (see, for example, p. 1145, col. 2). It is noted that although human ES cells may not be efficiently cloned this does not provide sufficient guidance to show that a human ES cell line could not reasonably be produced, given the teachings of the art. The requirement under §103 requires a reasonable, but not absolute, expectation of success. Applicants' arguments are directed to the inefficiency of production of a human ES cell line from a single ES cell, whereas the claims do not require a clonal hES cell line, and further, although

the screening procedure to isolate single human ES cells that undergo homologous recombination may be tedious and inefficient, this does not provide guidance for an unreasonable expectation of success. Additionally, the Examiner notes that the Zwaka reference specifically teaches using electroporation in order to produce human ES cells with a specific homologous recombination event (see Abstract, and p. 319-320, bridging paragraph). Thus, Zwaka provides evidence to show that using electroporation, human ES cells can be made with specific mutations using homologous recombination. Applicants' arguments regarding the major modifications needed for performing homologous recombination in human ES cells are not specifically defined, and therefore, in view of the evidence provided by the Zwaka reference, the Examiner maintains that the combination of the cited art of record is sufficient to arrive at the claimed invention with a reasonable expectation of success.

Rejection

Ratcliff teach the specific disruption of the cftr gene at the endogenous locus in mouse ES cells by gene targeting (see Abstract). Ratcliff teach that utilizing these mouse ES cells, transgenic animals can be produced to study pathophysiology and testing of new therapeutic drugs.

Ratcliff do not specifically teach human embryonic stem cells, or methods of using such cells in *in vitro* assays. However, prior to the time of the claimed invention, Thomson teach human embryonic stem cells, and teach that genetic modifications could be produced in ES cells, for reducing or combating immune rejection (p. 1147, 1st col). Thomson further teach the production of cell lines from the human ES cells. Thomson teach that human ES cells can be differentiated by allowing the cells to grow to confluence and pile up (production of embryoid bodies, see p. 1146, col. 1, 2nd ¶). Additionally, Thomson teach that human ES cells would be valuable in studies of development and function of tissues that differ between

mice and humans, and that screens based upon the *in vitro* differentiation to specific lineages could identify gene targets for new drugs (see p. 1146, col. 2-3, bridging ¶).

Thomson do not specifically teach the *in vitro* assay steps required by the claims. However, prior to the time of filing, the '659 document teaches methods for identifying candidate agents for treating conditions associated with motor neuron degeneration by obtaining embryonic stem cells, wherein the stem cells contain a mutation in a specific gene, contacting the ES cells with retinonic acid to differentiate the cells into neural progenitor cells, and determining the effect of an agent for use in treatment of a condition associated with motor neuron degeneration. See claim 1.

Accordingly, it would have been obvious to one of ordinary skill in the art, to utilize the technology to produce specific disruptions in mouse ES cells and apply this technology to human ES cells, and then utilize the resultant cells in methods of screening agents suitable for treating a disorder, such as the methods taught by the '659 document, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of Thomson's teachings who suggest producing genetic modifications in ES cells, and that human ES cells could be used for screening methods *in vitro* and the '659 document provide guidance with regard to the specific steps. Additionally, Elsea provide further guidance to show that various mouse models of human diseases, such as metachromatic leukodystrophy, do not produce a biochemical model that reproduces clinical symptoms (see Abstract) and therefore show a need in the art to produce cells that could be used for screening various human diseases using human cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 83-84 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ratcliff (**Transgenic Res.**, 1: 177-181, 1992, IDS) when taken with Thomson *et al.* (**Science**, 282: 1145-1147, November 6, 1998) in further view of Elsea *et al.* (**ILAR Journal**, 43(2): 66-79, 2002) as applied to claims 52, 55, 56, 58-60, 74, 75, 78-80, 82 above, and further in view of PGPub US 2005/0054092 A1.

Applicants provide the same arguments as the rejection above. The Examiner has addressed these arguments above.

Ratcliff, Thomson, Elsea are described above. They do not specifically teach isolating lineage specific cells by mechanical separation of cells tissues and/or tissue-like structures contained within the embryoid body. However, prior to the time of the claimed invention, the '092 document teaches that suspensions of pPS derived cells can be further enriched with desirable characteristics, such as mechanical separation or cell sorting (p. 8, ¶117). In particular, the '092 document teaches that FACS sorting can be used (p. 10, ¶144).

Accordingly, it would have been obvious for one of skill in the art to modify the methods taught by Ratcliff, Thomson and Elsea, to include a step of isolating a lineage-specific cell, utilizing either cell sorting, such as FACS sorting, or mechnical isolation techniques, as taught by the '092 document with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification in order to have a purified population of cells for *in vitro* screening assays.

Claims 57, 81 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ratcliff (**Transgenic Res.**, 1: 177-181, 1992, IDS) when taken with Thomson *et al.* (**Science**, 282: 1145-1147, November 6, 1998) in further view of Elsea *et al.* (**ILAR Journal**, 43(2): 66-79, 2002)as applied to claims 52, 55, 56, 58-60, 74, 75, 78-80, 82 above, and further in view of US Pat. No. 5,972,955.

Applicants provide the same arguments as the rejection above. The Examiner has addressed these arguments above.

Ratcliff, Thomson, Elsea are described above. They do not specifically teach a sequence, such as those recited in claims 57 and 81. However, prior to the time of filing, the '995 reference teaches an exact match of SEQ ID NO: 24 (see alignment, presented previously).

Accordingly, it would have been obvious for the ordinary skilled artisan to modify the teachings of Ratcliff, Thomson and Elsea, to produce human ES cells carrying a mutation, such as the W1282X as set forth in SEQ ID NO: 24, associated with cystic fibrosis, with a reasonable expectation of success. One of ordinary skill would have been motivated to make this modification in order to produce ES cells that could then be used for screen therapeutic agents for treatment of cystic fibrosis.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632